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Cross-correlation enhanced stability in a tumor cell growth model with immune surveillance driven by cross-correlated noises

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Abstract
The transient properties of a tumor cell growth model with immune surveillance driven by cross-correlated multiplicative and additive noises are investigated. The explicit expression of extinction rate from the state of a stable tumor to the state of extinction is obtained. Based on the numerical computations, we find the following: (i) the intensity of multiplicative noise D and the intensity of additive noise α enhance the extinction rate for the case of $\lambda \leqslant 0$ (i.e. λ denotes cross-correlation intensity between two noises), but for the case of $\lambda > 0$, a critical noise intensity D or α exists at which the extinction rate is the smallest; D and α at first weaken the extinction rate and then enhance it. (ii) The immune rate β and the cross-correlation intensity λ play opposite roles on the extinction rate, i.e. β enhances the extinction rate of the tumor cell, while λ weakens the extinction rate of the tumor cell. Namely, the immune rate can enhance the extinction of the tumor cell and the cross-correlation between two noises can enhance stability of the cancer state.

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1. Introduction

In recent years, the law of tumor cell growth has been investigated extensively both in the area of theory or the one of experiment in a large variety of physical, chemical, biological systems [1, 2]. There are several models for describing tumor growth, such as the screened Eden model [3], Gompertzian growth model [4], self-limiting growth model [5], feedback model [6] and predator–prey model [7–11], etc. Scientists have tried to find exact measures to control tumors and cure cancers, and showed that there is an interesting and significant case for immunotherapy in tumor treatments [12–14]. The cell-mediated immune surveillance against cancer is also one of the effects which may be described in terms of a 'predator–prey' system; the population of tumor cells here plays the role of 'preys' whereas the immune cells are regarded as 'predators'. The activity of the predator in a certain territory, or the activity of immune cells in tissue, resembles the mode of action of enzymes or catalysts in a chemical reaction, where the enzymes transform substrates in a continuous manner without destroying themselves. The constant immune cell population is assumed to act in a similar way, binding the tumor cells and subsequently releasing them so that they are unable to replicate [15].

More recently, the model of the tumor cell growth with immune response has attracted a lot of attention in the biological system [15, 16]. For example, the simplest model which describes phase transition in the tumor cell growth model with immune surveillance is given by a Langevin equation with additive noise [17, 18]. Then, Zhong *et al* investigated pure multiplicative stochastic resonance and non-equilibrium phase transition in this system with multiplicative Gaussian white noise [19, 20]. The works mentioned above are only concerned with a single noise case, but the system is always disturbed by random fluctuations of the external environment (e.g. host tissue pressure, immune response, etc) and the intrinsic thermal fluctuations simultaneously, and in certain situations the two fluctuations may have a common origin and thus may be correlated with each other as well [21]. The effects of cross-correlation between two noises on the transient properties of the nonlinear system have been applied to many fields, such as a bistable system [22, 23], laser system [24], biological system [25] and so on. However, the effects of cross-correlation between two noises on the transient properties of the tumor cell growth model with immune surveillance driven by cross-correlated noises have not yet been discussed. Therefore, in order to understand further the dynamics properties of the tumor cell growth model with immune surveillance driven by cross-correlated noises, the extinction rate of the system from the state of a stable tumor to the state of extinction needs to be investigated.

This paper is arranged as follows: in section 2, using the steepest descent method, the explicit expression of the extinction rate from the state of a stable tumor to the state of extinction is derived. The effects of the multiplicative noise intensity D, the additive noise intensity α, the immune rate β and the cross-correlation intensity λ on the extinction rate have been discussed. Finally, discussions and conclusions end the paper.

2. The extinction rate for the tumor cell growth model with immune surveillance

We consider the growth of the tumor under immune surveillance against cancer using the logistic growth model [26]. The model is

$$\frac{\mathrm{d}x}{\mathrm{d}t} = x(1-\theta x) - \beta\frac{x}{x+1}, \tag{1}$$

where x is the population of the tumor cells, β is the immune rate and θ is the constant parameter. If we consider the environmental fluctuations (e.g. temperature, pH, ionic strength, drugs, etc), these can influence the tumor mass directly as well as alter the tumor immune rate. In other words, the fluctuation of these factors affects the immune rate β generating multiplicative noise. At the same time, some factors, such as drugs and radiotherapy, restrain the number of tumor cells, give rise to an additive noise. As a result, we obtain

$$\frac{\mathrm{d}x}{\mathrm{d}t} = x(1-\theta x) - \beta\frac{x}{x+1} - \frac{x}{x+1}\xi(t) + \eta(t), \tag{2}$$

where $\xi(t)$ and $\eta(t)$ are Gaussian white noises and their statistical properties are given by

$$\begin{aligned} \langle\xi(t)\rangle &= 0, \qquad \langle\xi(t)\xi(t')\rangle = 2D\delta(t-t'), \\ \langle\eta(t)\rangle &= 0, \qquad \langle\eta(t)\eta(t')\rangle = 2\alpha\delta(t-t'), \end{aligned} \tag{3}$$

in which D is the intensity of the multiplicative noise and α is the intensity of the additive noise. In [15, 16], $\xi(t)$ in equation (2) is a dichotomous colored noise, but here $\xi(t)$ is Gaussian white noise and there is a cross-correlation between $\xi(t)$ and $\eta(t)$. The correlation form between the two noises is assumed to be as follows:

$$\langle \xi(t)\eta(t')\rangle = \langle \eta(t)\xi(t')\rangle = 2\lambda\sqrt{D\alpha}\,\delta(t-t'), \tag{4}$$

where λ denotes the intensity of cross-correlation between $\xi(t)$ and $\eta(t)$. The deterministic potential corresponding to equation (2) is

$$V(x) = -\frac{x^2}{2} + \frac{\theta x^3}{3} + \beta x - \beta \ln(x+1), \tag{5}$$

which has two steady stable states $x_1 = 0$, $x_2 = (1-\theta+\sqrt{(1+\theta)^2-4\beta\theta})/2\theta$, and one unstable steady state $x_u = (1-\theta-\sqrt{(1+\theta)^2-4\beta\theta})/2\theta$.

Considering the stochastic process in the steady-state regime, the approximate Fokker–Planck equation corresponding to equations (2) and (3) is derived by using the Novikov theorem [27, 28] and Fox approach [29], which is as follows [30, 31]:

$$\frac{\partial P(x,t)}{\partial t} = -\frac{\partial}{\partial x}A(x)P(x,t) + \frac{\partial^2}{\partial x^2}B(x)P(x,t), \tag{6}$$

where

$$\begin{aligned} A(x) &= x(1-\theta x) - \beta\frac{x}{x+1} + \frac{Dx}{(x+1)^3} - \frac{\lambda\sqrt{D\alpha}}{(x+1)^2},\\ B(x) &= D\left(\frac{x}{x+1}\right)^2 - 2\lambda\sqrt{D\alpha}\frac{x}{x+1} + \alpha. \end{aligned} \tag{7}$$

From equations (6) and (7), the stationary probability distribution function $P_{\text{st}}(x)$ can be derived as

$$P_{\text{st}}(x) = \frac{N}{B^{1/2}(x)}\exp\left[-\frac{U(x)}{D}\right], \tag{8}$$

where $U(x)$ is the generalized potential, given by

$$\begin{aligned} U(x) &= -\int^x \frac{x(1-\theta x) - \beta\frac{x}{x+1}}{\left(\frac{x}{x+1}\right)^2 - 2\lambda\sqrt{R}\frac{x}{x+1} + R}\,\mathrm{d}x\\ &= \frac{\theta}{3m}x^3 + \frac{1}{2m}\left(2\theta - 1 - \frac{n}{m}\theta\right)x^2 - \frac{\gamma_1}{m}x + \frac{1}{2m}\left(\gamma_2 - \frac{n}{m}\gamma_1\right)\ln\left|x^2 + \frac{n}{m}x + \frac{R}{m}\right|\\ &\quad - \frac{2\gamma_3}{\sqrt{4mR-n^2}}\arctan\frac{2mx+n}{\sqrt{4mR-n^2}}, \end{aligned} \tag{9}$$

in which

$$\begin{aligned} &R = \alpha/D, \qquad m = 1 - 2\lambda\sqrt{R} + R, \qquad n = 2(R - \lambda\sqrt{R}),\\ &\gamma_1 = \beta - 2 + \theta - \frac{R}{m}\theta - \left(2\theta - 1 - \frac{n}{m}\theta\right)\frac{n}{m},\\ &\gamma_2 = \beta - 1 - \left(2\theta - 1 - \frac{n}{m}\theta\right)\frac{R}{m},\\ &\gamma_3 = \frac{R\gamma_1}{m} + \frac{n}{2m}\left(\gamma_2 - \frac{n}{m}\gamma_1\right). \end{aligned} \tag{10}$$

Using the steepest descent method [32–34], the explicit expression for the mean extinction time of the process $x(t)$ to reach the the state of extinction x_1 with the initial condition

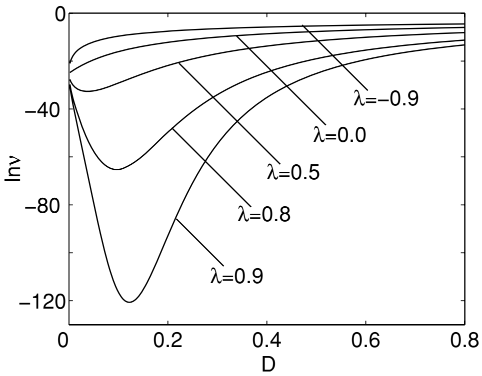

Figure 1. Curves of escape rate ν versus multiplicative noise strength D for different values of λ with $\alpha = 0.1, \theta = 0.1$ and $\beta = 2.26$. λ takes respectively −0.9, 0, 0.5, 0.8 and 0.9 from top to bottom.

$x(t = 0) = x_2$ (the state of a stable tumor) is given by the Kramers-like formula

$$T = \frac{2\pi}{\sqrt{|V''(x_u)V''(x_2)|}} \exp\left[\frac{U(x_u) - U(x_2)}{D}\right]. \tag{11}$$

Note that the above result is valid only when the intensity of two types of noises, measured by D and α, is small in comparison with the energy barrier height $\triangle U = |U(x_u) - U(x_2)|$ [25, 35]. It provides restriction on the parameters (such as θ, β, D, α and λ). The following results in this study are restricted in valid regions. Then, we obtain the extinction rate from the state of a stable tumor to the state of extinction as the following formula [36]:

$$\nu = T^{-1} = \frac{\sqrt{|V''(x_u)V''(x_2)|}}{2\pi} \exp\left[\frac{U(x_2) - U(x_u)}{D}\right], \tag{12}$$

where V'' is the second derivative of V with respect to x.

3. Discussions and conclusions

Equation (2) represents a physical model of a tumor cell growth system with immune surveillance driven by cross-correlated multiplicative and additive noises corresponding to the deterministic potential $V(x)$ (equation (5)); $V(x)$ has two steady states x_1 and x_2, which represent the state of extinction, where no tumor cells are present, and the state of stable tumor, where its density does not increase but stay at a certain constant level. Environmental fluctuations present in the system can induce transitions between those two states. From this point of view, it is interesting to study the extinction rate from the state of a stable tumor to the state of extinction. We want to find out how the extinction rate can be changed by varying the noise parameters, such as the noise intensity or the immune rate. The extinction rate distribution curves of the tumor cell growth system are plotted in figures 1–4.

Figures 1 and 2 show the extinction rate as a function of the multiplicative noise intensity D and as a function of the additive noise intensity α for different values of the cross-correlation intensity λ of noises, respectively. From the physics point of view, one can see that for fixed θ, β, α and D, the generalized force

$$F = -\frac{dU(x)}{dx} = \frac{x(1-\theta x) - \beta\frac{x}{x+1}}{\left(\frac{x}{x+1}\right)^2 - 2\lambda\sqrt{\alpha/D}\frac{x}{x+1} + \alpha/D} \tag{13}$$

increases within the interval $0 \leqslant x_1 < x_2$, when increasing the value of λ. Also, the height

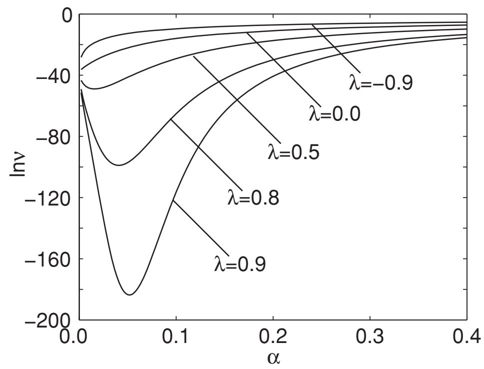

Figure 2. Curves of escape rate ν versus additive noise strength α for different values of λ with $D = 0.1$, $\theta = 0.1$ and $\beta = 2.26$. λ takes respectively -0.9, 0, 0.5, 0.8 and 0.9 from top to bottom.

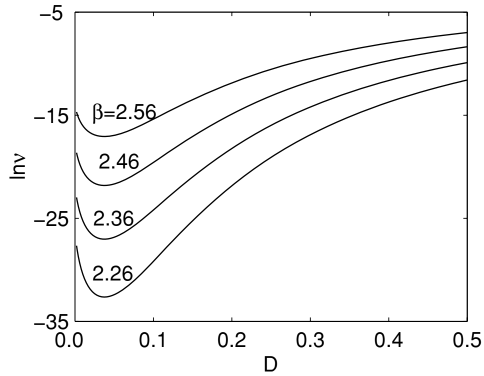

Figure 3. Curves of escape rate ν versus multiplicative noise strength D for different values of β with $\alpha = 0.1$, $\lambda = 0.5$ and $\theta = 0.1$. β takes respectively 2.56, 2.46, 2.36 and 2.26 from top to bottom.

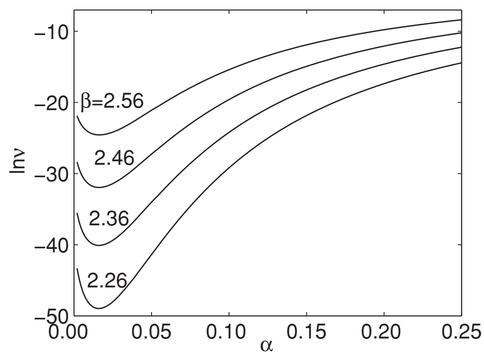

Figure 4. Curves of escape rate ν versus additive noise strength α for different values of λ with $D = 0.1$, $\lambda = 0.5$ and $\theta = 0.1$. β takes respectively 2.56, 2.46, 2.36 and 2.26 from top to bottom.

of the barrier for the transition from x_2 to x_1 increases. Thus, this causes an increase in the mean extinction time and consequently the extinction rate decreases with increasing λ, as shown in figures 1 and 2. In consideration of the denominator of the expression (13),

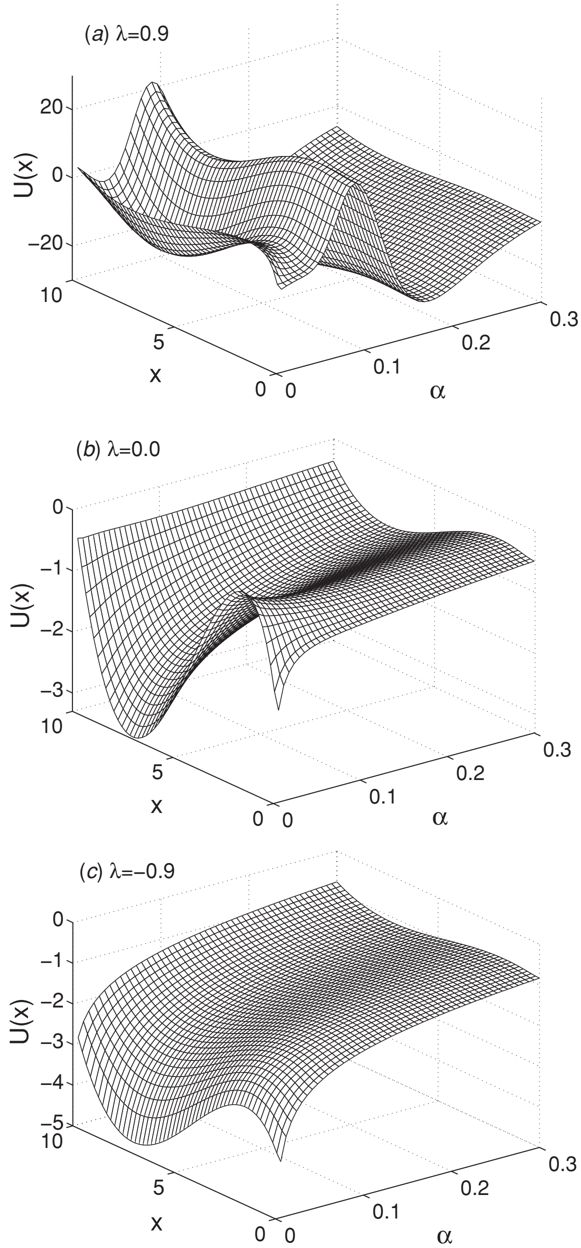

Figure 5. Three-dimensional curve of the generalized potential $U(x)$ versus x and α with $D = 0.1$, $\theta = 0.1$ and $\beta = 2.26$. (a) $\lambda = 0.9$; (b) $\lambda = 0.0$; (c) $\lambda = -0.9$.

$(x/(x+1) - \lambda\sqrt{\alpha/D})^2 + \alpha(1-\lambda^2)/D$ has a minimum at $x_c = \frac{\lambda\sqrt{\alpha/D}}{1-\lambda\sqrt{\alpha/D}}$ for the case of $\lambda > 0$. It is obvious that the generalized force exhibits one maximum value within the interval $0 \leqslant x_1 < x_2$ for the case of $\lambda > 0$. Also, the height of the barrier for the transition from x_2 to x_1 exhibits one maximum value. Hence, this causes one maximum value for the mean extinction time and consequently the extinction rate exhibits one minimum value (see $\lambda = 0.5$, $\lambda = 0.8$ and $\lambda = 0.9$ in figures 1 and 2). However, for the cases of $\lambda \leqslant 0$, $x_c = \frac{\lambda\sqrt{\alpha/D}}{1-\lambda\sqrt{\alpha/D}} \leqslant 0$, since

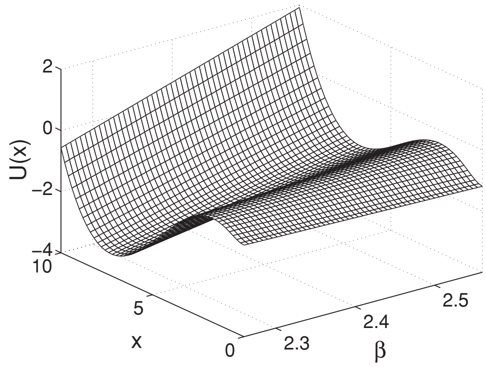

Figure 6. Three-dimensional curve of the generalized potential $U(x)$ versus x and β with $\alpha = 0.1, \lambda = 0.5, \theta = 0.1$ and $D = 0.1$.

x cannot be negative, the denominator of expression (13) monotonously increases, and the generalized force monotonously decreases. Also, the height of the barrier for the transition from x_2 to x_1 decreases. This in turn causes a decrease for the mean extinction time and consequently the extinction rate increases (see $\lambda = -0.9$, and $\lambda = 0.0$ in figures 1 and 2). Our results showed that D and α can weaken the extinction rate of the system firstly and then enhance it for the case of $\lambda > 0$; a critical noise intensity D or α exists at which the extinction rate induced by noises is the smallest. However, for the case of $\lambda \leqslant 0$, D and α enhance the extinction rate.

For fixed θ, α, D and λ (i.e. see figures 3 and 4), the extinction rate is increased with the increasing immune rate β. From the aspect of physics, it is obvious that the generalized force decreases within the interval $0 \leqslant x_1 < x_2$ with increasing β (see equation (13)). Hence, the height of the barrier decreases within the interval $0 \leqslant x_1 < x_2$ with increasing β. This in turn causes the extinction of the tumor cell with the increasing immune rate β.

In order to provide some insight into the above-mentioned phenomenon, we plot the three-dimensional curves of the generalized potential $U(x)$ versus x and α (or β) in figures 5(a–c) and 6. The behavior of the three-dimensional curves of $U(x)$ versus x and D is similar to that of $U(x)$ versus x and α. For brevity, the three-dimensional curves of $U(x)$ versus x and D are not presented in this paper. Obviously, the generalized potential has two stable states, and their minimum is obtained from $A(x) - B'(x) = 0$. The positions of the potential minimum, x_1 and x_2, shown in figures 5(a–c) and 6, are regarded as the state of extinction and the state of stable tumor, respectively. The generalized potential is an asymmetrical bistable potential well and its values at x_1 and x_2 change with the noise intensity α or the immune rate β, and then we can define the difference between the potential well at x_1 and that at x_2 as $|U(x_1) - U(x_2)|$. The larger the difference between the potential well, the smaller the transition from x_2 to x_1, and vice versa. When the cross-correlation intensity $\lambda > 0$ (see $\lambda = 0.9$ in figure 5(a)), as the intensity of noise α increases, the difference between the potential well increases firstly and then decreases. However, for the case of $\lambda \leqslant 0$ (see $\lambda = 0.0$ and -0.9 in figures 5(b), (c)), the difference between the potential well decreases as α increases. When the cross-correlation intensity λ is fixed (see figure 6), as the immune rate β increases, the difference between the potential well decreases.

In conclusion, the intensity of noises D and α enhance the extinction rate for the case of $\lambda \leqslant 0$; however, for the case of $\lambda > 0$, D and α weaken the extinction rate firstly and then enhance it. The immune rate β and the cross-correlation intensity λ play opposite roles on the extinction rate, i.e β enhances the extinction of the tumor cell, while λ weakens the extinction rate of the tumor cell; in other words, cross-correlation between two noises can enhance the stability of the cancer state.

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